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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,452	05/05/2006	Hengyuan Lang	34056-US-PCT	9887

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EXAMINER	
WILLIS, DOUGLAS M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
12/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,452	LANG ET AL.	
	Examiner	Art Unit	
	DOUGLAS M. WILLIS	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-61* is/are pending in the application.

4a) Of the above claim(s) *6-10,16-18,38-53 and 58-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,12-15,19-37 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01-20-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

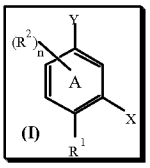
Status of the Claims / Priority

Claims 1-10 and 12-61 are pending in the current application. According to the *Amendments to the Claims*, filed November 17, 2008, claims 1, 18, 37 and 58-61 were amended and claim 11 was canceled. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/US2004/023726, filed July 23, 2004, which claims priority under 35 U.S.C. § 119(e) to US Provisional Application No. 60/490,096, filed July 25, 2003.

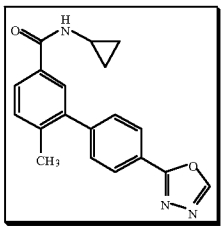
Restrictions / Election of Species

The previous *Requirement for Restriction / Election of Species*, mailed May 16, 2008, is hereby clarified as follows with regard to the claims readable on Group II: Group II reads on claims 1-5, 12-15, 19-37 and 54-57, and not on claims 1-37 and 54-57, as previously stated.

Applicant's provisional election of the following, without traverse, in the reply filed on



November 17, 2008, is acknowledged: a) Group II - claims 1-5, 12-15, 19-37 and 54-57; and b) substituted benzene of formula (I) - p. 33, example 1, shown right below, and hereafter referred to as *N*-cyclopropyl-6-methyl-4'-(1,3,4-oxadiazol-2-yl)biphenyl-3-carboxamide, where n = 0; R^1 = -CH_3 (lower alkyl); Y = -L-R^3, wherein L = -C(=O)NH- and R^3 = -cycloalkyl; and X = -Ph-P, wherein P = -R^{15}, where R^{15} = -oxadiazolyl (heteroaryl). Claims 1-5, 12, 13, 15, 27-30, 32-37 and 54-57 read on the elected species. Affirmation of this election must be made by applicant in replying to this Office action.



The requirement is still deemed proper and is therefore made FINAL.

Claims 6-10, 16-18, 38-53 and 58-61 were withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to a nonelected or canceled invention, there being no allowable generic or linking claim.

Thus, a first Office action on the merits of claims 1-5, 12-15, 19-37 and 54-57 is contained within.

Information Disclosure Statement

The information disclosure statement, filed January 20, 2006, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the foreign references (WO) are not provided. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification - Disclosure

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase

"Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
  (1) Field of the Invention.
  (2) Description of Related Art (including information disclosed under 37 CFR 1.97 and 1.98).
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825).

Applicant is advised to format the specification according to 37 CFR 1.77(b) above. Revisions should particularly include and/or address sections (b-e) and (h). Appropriate correction is required.

Specification - Title

Applicant is reminded of the proper content of the title of the invention.

The title of the invention should be brief, but technically accurate and descriptive, preferably from two to seven words. See 37 CFR 1.72(a) and MPEP § 606.

The title of the invention is not technically accurate and descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. In the revised title, the examiner suggests identifying the class/type of compounds allegedly responsible for P-38 kinase inhibition.

Specification - Abstract

Applicant is reminded of the proper content of an abstract of the disclosure.

With regard particularly to chemical patents, for compounds or compositions, the general nature of the compound or composition should be given as well as the use thereof, e.g., "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example, unless variations are necessary. See MPEP § 608.01(b), Section B.

The abstract of the disclosure is objected to because: a) it neither provides for the general nature of the compound(s) nor exemplifies any members or formulae illustrative of its class; and b) *Y* and *X* should be amended to reflect the scope of the *Requirement for Restriction / Election of Species*, mailed on May 16, 2008. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 1 is objected to because of the following informalities: the recited definitions *heterocycle* and *substituted heterocycle*, with respect to R^3, should be *heterocyclyl* and substituted *heterocyclyl*, respectively. Appropriate correction is required.

Claim 5 is objected to because of the following informalities: the limitation *the compound of any of claim 1* is improper. Appropriate correction is required.

The examiner suggests deleting the phrase *any of* to overcome this objection.

Claim 34 is objected to because of the following informalities: the conjunction *and* is omitted between the recited definitions *heteroaryl* and *substituted heteroaryl*. Appropriate

correction is required.

Claim 55 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. The intended use of a pharmaceutical composition of claim 54, in a formulation for single dosage administration, is not found to be further limiting since the intended use is not given patentable weight.

Claim 57 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. The intended use of an article of manufacture comprising a label, in treating, preventing or ameliorating one or more symptoms of p38 kinase-mediated diseases or disorders, is not found to be further limiting since the intended use is not given patentable weight.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Substituted benzenes and pharmaceutical compositions of the formula (I)

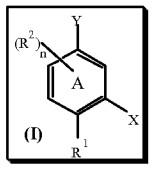
Claims 1-5, 12-15, 19-36 and 54-57 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for substituted benzenes and pharmaceutical compositions of the formula (I), where R^1 = -halogen or -lower alkyl; R^2 = -H or -alkyl; R^3 = -H,

-alkyl, -substituted alkyl or -cycloalkyl; R^6 = -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V = $-M-R^{10}$, does not reasonably provide enablement for substituted benzenes and pharmaceutical compositions of the formula (I), where $R^1 \neq$ -halogen or -lower alkyl; $R^2 \neq$ -H or -alkyl; $R^3 \neq$ -H, -alkyl, -substituted alkyl or -cycloalkyl; $R^6 \neq$ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V $\neq$ $-M-R^{10}$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention(s) commensurate in scope with these claims. Substituted benzenes and pharmaceutical compositions of the formula (I), where $R^1 \neq$ -halogen or -lower alkyl; $R^2 \neq$ -H or -alkyl; $R^3 \neq$ -H, -alkyl, -substituted alkyl or -cycloalkyl; $R^6 \neq$ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V $\neq$ $-M-R^{10}$, as recited in claim 1, have not been adequately enabled in the specification to allow any person having ordinary skill in the art, at the time this invention was made, to make and use substituted benzenes and pharmaceutical compositions of the formula (I), where $R^1 \neq$ -halogen or -lower alkyl; $R^2 \neq$ -H or -alkyl; $R^3 \neq$ -H, -alkyl, -substituted alkyl or -cycloalkyl; $R^6 \neq$ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V $\neq$ $-M-R^{10}$.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of substituted benzenes and pharmaceutical compositions of the formula (I), shown right;



(b) *Nature of the invention* - the nature of the invention is evaluation of substituted benzenes and pharmaceutical compositions of the formula (I) and the pharmacokinetic behavior of these substances in the human body as P-38 kinase inhibitors;

(c) *State of the prior art* - *Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical trials (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, p. 205);

(d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's substituted benzenes and pharmaceutical compositions of the formula (I), where R^1 ≠ -halogen or -lower alkyl; R^2 ≠ -H or -alkyl; R^3 ≠ -H, -alkyl, -substituted alkyl or -cycloalkyl; R^6 ≠ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V ≠ $-M-R^{10}$, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;

(e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (*In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Dörwald, which has extreme relevance to the synthesis of substituted benzenes and pharmaceutical compositions of the formula (I), where R^1 ≠ -halogen or -lower alkyl; R^2 ≠ -H or -alkyl; R^3 ≠ -H, -alkyl, -substituted alkyl or -cycloalkyl; R^6 ≠ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V ≠ $-M-R^{10}$ (Dörwald, F. Zaragoza. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, Preface):

Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.

Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for

instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.

Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).

(f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and using substituted benzenes and pharmaceutical compositions of the formula (I), where $R^1 \neq$ -halogen or -lower alkyl; $R^2 \neq$ -H or -alkyl; $R^3 \neq$ -H, -alkyl, -substituted alkyl or -cycloalkyl; $R^6 \neq$ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V ≠ -M-R^{10};

(g) *Existence of working examples* - applicant has provided sufficient guidance to make and use substituted benzenes and pharmaceutical compositions of the formula (I), where R^1 = -halogen or -lower alkyl; R^2 = -H or -alkyl; R^3 = -H, -alkyl, -substituted alkyl or -cycloalkyl; R^6 = -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V = -M-R^{10}; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of substituted benzenes and pharmaceutical compositions of the formula (I), where $R^1 \neq$ -halogen or -lower alkyl; $R^2 \neq$ -H or -alkyl; $R^3 \neq$ -H, -alkyl, -substituted alkyl or -cycloalkyl; $R^6 \neq$ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V ≠ -M-R^{10}. The specification lacks working examples of substituted benzenes and pharmaceutical compositions of the formula (I), where $R^1 \neq$ -halogen or -lower alkyl; $R^2 \neq$ -H or -alkyl; $R^3 \neq$ -H, -alkyl, -substituted alkyl or -cycloalkyl; $R^6 \neq$ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and V ≠ -M-R^{10}.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP § 608.01(p).

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, pp. 205-213).

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and using substituted benzenes and pharmaceutical compositions of the formula (I), where $R^1 \neq$ -halogen or -lower alkyl; $R^2 \neq$ -H or -alkyl; $R^3 \neq$ -H, -alkyl, -substituted alkyl or -cycloalkyl; $R^6 \neq$ -H, -alkyl, $-NH_2$, $-NMe_2$, or $-NHC(=O)R^4$; and $V \neq$ $-M-R^{10}$, is clearly justified.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 12-15, 19-36 and 54-57 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation *...a pharmaceutically acceptable derivative thereof* in *line 3* of the claim. The term *derivative*: a) is defined by the Merriam-Webster Online Dictionary and taken by one having ordinary skill in the art to mean *a substance that can be made from another substance*; and b) signifies the advent of a *product-by-process* claim. Applicants fail to define any processes giving rise to such a *derivative*, rendering uncertainty as to what the true structure of such a *derivative* would be. Consequently, the recited structural limitation of formula I, which is covered under the rubric of *derivative,* is simply indefinite.

The examiner suggests deletion of the phrase *a pharmaceutically acceptable derivative thereof* to overcome this rejection.

Claims 1-5, 12-15, 19-27, 31-36 and 54-57 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation *n is 0 or 1* in *line 8 on p. 4* of the claim. The examiner asserts that *n* may be 0, 1, 2 or 3, if R^2 is independently selected from hydrogen, as recited in the context of claim 2. Thus, one of ordinary skill in the art, would not be reasonably apprised of the scope of *n*.

The examiner suggests amending the definition of the variable *n* or removing hydrogen from the list of substituents recited for R^2 to overcome this rejection. Furthermore, based on the

recited structural formula (I) in claim 1, the examiner asserts that one of ordinary skill in the art would reasonably ascertain that if a recited substituent is not present (i.e. *n = 0*), then a hydrogen atom must be present at the relative positions of the benzene ring.

Claims 22 and 23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites the limitation *the compound of claim 1, wherein* R^{10} *is alkoxyaralkyl* in *lines 1 and 2* of the claim. In claim 1, R^{10} is recited as $-(CH_2)_t-D-(CH_2)_e-R^{13}$, wherein *t* may be *1*, *D* may be *-O-* and *e* may be *1*; however, since R^{13} may not be aryl, nevertheless phenyl, the examiner is uncertain as to how one of ordinary skill in the art would envision *methoxybenzyl*, as recited within the context of claim 23. Applicant should note that *methoxybenzyl* could be construed by one of ordinary skill in the art as $-CH_2-O-CH_2Ph$, which may be referred to as *methoxybenzyl* or benzyloxymethyl. Thus, one of ordinary skill in the art, would not be reasonably apprised of the scope of R^{10}.

The examiner suggests that if applicant's intent is to have the alkoxy group attached to the -Ph ring of the *alkoxyaralkyl* substituent, either a position of such attachment should be duly noted or clarity should be recited in the claim.

Claim 56 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56 recites the limitation *...the pharmaceutical composition of claim 54, further comprising one or more of the following: rapamycin, or derivatives thereof* in *line 8* of the claim.

The term *derivative*: a) is defined by the Merriam-Webster Online Dictionary and taken by one having ordinary skill in the art to mean *a substance that can be made from another substance*; and b) signifies the advent of a *product-by-process* claim. Applicants fail to define any processes giving rise to such *derivatives*, rendering uncertainty as to what the true structure of such *derivatives* would be. Consequently, the recited structural limitations of formula I, which are covered under the rubric of *derivatives,* is simply indefinite.

The examiner suggests deletion of the phrase *or derivatives thereof* to overcome this rejection.

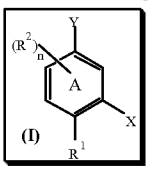
Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 12, 13, 15, 27, 32 and 54-57 are rejected under 35 U.S.C. § 102(b) as being anticipated by Tang, et al. in WO 01/094312.

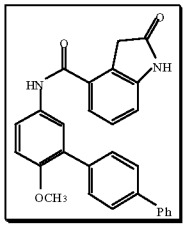
The instant application recites substituted benzenes and pharmaceutical compositions of



the formula (I), shown to the left, where n = 0; R^1 = -methoxy; R^2 = -H; Y = -L-R^3, wherein L = -NHC(=O)- and R^3 = -heterocyclyl; and X = -Ph-P, wherein P = -R^{15},

where R^{15} = -aryl, as P-38 kinase inhibitors.

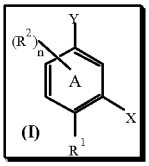
Tang, et al. (WO 01/094312) teaches substituted benzenes and pharmaceutical



compositions of the formula (I), shown to the left below, where n = 0; R^1 = -OCH_3; R^2 = -H; Y = -L-R^3, wherein L = -NHC(=O)- and R^3 = -indolinonyl; and X = -Ph-P, wherein P = -R^{15}, where R^{15} = -phenyl, as protein kinase inhibitors [p. 29, lines 7-8 and p. 194, lines 19-20; pharmaceutical compositions - p. 37, lines 3-7; formulation, routes of administration and dosage forms - p. 53, line 16 - p. 58, line 24; and packaging - p. 60, lines 1-16].

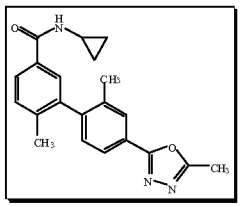
Claims 1-5, 12-15, 27-36 and 54-56 are rejected under 35 U.S.C. § 102(e) as being anticipated by Angell, et al. in WO 03/093248.

The instant application recites substituted benzenes and pharmaceutical compositions of



the formula (I), shown to the left, where n = 1; R^1 = -lower alkyl; R^2 = -alkyl; Y = -L-R^3, wherein L = -C(=O)NH- and R^3 = -cycloalkyl; and X = -Ph-P, wherein P = -R^{15}, where R^{15} = -heteroaryl, as P-38 kinase inhibitors.

Angell, et al. (WO 03/093248), as cited on the IDS, teaches substituted benzenes and pharmaceutical compositions of the formula (I), shown to the right, where n = 1; R^1 = -CH_3; R^2 = -CH_3; Y = -L-R^3, wherein L = -C(=O)NH- and R^3 = -cyclopropyl; and X = -Ph-P, wherein P = -R^{15}, where R^{15} = -oxadiazolyl,



optionally substituted with one R^{12}, wherein R^{12} = -R^{10}, where R^{10} = -CH_3 (alkyl), as P-38 kinase inhibitors [p. 39, example 6, lines 11-19; simple pharmaceutical compositions, administration, dosage forms and delivery systems - p. 12, line 10 - p. 15, line 39; and complex pharmaceutical compositions - p. 18, lines 5-26].

Furthermore, although not explicitly discussed herein, applicant is advised to note that this reference is replete with species representative of substituted benzenes and pharmaceutical compositions of the formula (I). Consequently, any amendments to the claims to overcome rejections rendered under 35 U.S.C. § 102 should address this reference as a whole and should not be limited to the species discussed or disclosed explicitly herein.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

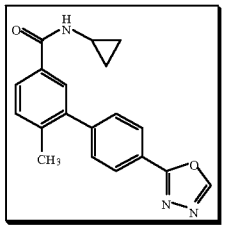
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

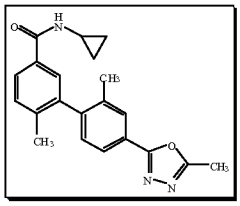
Claims 1-5, 12-15, 27-37 and 54-56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Angell, et al. in WO 03/093248, in view of Patani, et al. in *Chem. Rev.*, 96, **1996**, pp. 3147-3176.

The instant application recites substituted benzenes and pharmaceutical compositions of the formula (I), shown to the right, where n = 0; R^1 = -CH_3 (lower alkyl); R^2 = -H; Y = -L-R^3, wherein L = -C(=O)NH-



and R^3 = -cycloalkyl; and X = -Ph-P, wherein P = $-R^{15}$, where R^{15} = -oxadiazolyl (heteroaryl), as P-38 kinase inhibitors.

Angell, et al. (WO 03/093248), as cited on the IDS, teaches substituted benzenes and



pharmaceutical compositions of the formula (I), shown to the left, where n = 1; R^1 = $-CH_3$; R^2 = $-CH_3$; Y = -L-R^3, wherein L = -C(=O)NH- and R^3 = -cyclopropyl; and X = -Ph-P, wherein P = $-R^{15}$, where R^{15} = -oxadiazolyl, optionally substituted with one R^{12}, wherein R^{12} = $-R^{10}$, where R^{10} = $-CH_3$ (alkyl), as P-38 kinase inhibitors [p. 39, example 6, lines 11-19; simple pharmaceutical compositions, administration, dosage forms and delivery systems - p. 12, line 10 - p. 15, line 39; and complex pharmaceutical compositions - p. 18, lines 5-26]. Furthermore, in the genus disclosure, Angell discloses that R^2 may be hydrogen and R^{15} may be *optionally* substituted [R^2 - p. 1, line 21; and R^{15} - R^1 on p. 1, lines 14-20].

Patani, et al. (*Chem. Rev.*, 96, **1996**) teaches the relationship between $-CH_3$ groups and -H atoms as monovalent bioisosteres, which exert similar biological activity [p. 3148, column 1], via a direct adaptation of Grimm's Hydride Displacement Law [p. 3152, section A4; p. 3153, column 1, ¶ 2; p. 3153, Table 12, column 2].

The differences between the applicant's instantly recited substituted benzenes and pharmaceutical compositions of the formula (I) and Angell's substituted benzenes and pharmaceutical compositions of the formula (I) are: a) R^2 is a -H atom in the instantly recited substituted benzenes and pharmaceutical compositions of the formula (I), whereas R^2 is $-CH_3$ group in Angell's substituted benzenes and pharmaceutical compositions of the formula (I); and b) R^{15} is an unsubstituted oxadiazole ring in the instantly recited substituted benzenes and

pharmaceutical compositions of the formula (I), whereas R^{15} is an oxadiazole ring substituted with a -CH_3 group in Angell's substituted benzenes and pharmaceutical compositions of the formula (I).

Consequently, since: a) Angell teaches substituted benzenes and pharmaceutical compositions of the formula (I), where R^2 is a -CH_3 group and R^{15} is an oxadiazole ring substituted with a -CH_3 group; b) Angell teaches substituted benzenes and pharmaceutical compositions of the formula (I), where -CH_3 and -H are alternatively usable at R^2 and R^{15}; and c) Patani teaches the relationship between -CH_3 groups and -H atoms as monovalent bioisosteres, which exert similar biological activity, one having ordinary skill in the art, at the time this invention was made, would have been motivated to combine the teachings of Angell and Patani and: a) replace the -CH_3 groups at R^2 and R^{15}, respectively, in Angell's substituted benzenes and pharmaceutical compositions of the formula (I), with alternatively usable -H atoms, with a reasonable expectation of success and similar therapeutic activity, rendering claims 1-5, 12-15, 27-37 and 54-56 obvious.

Finally, although not explicitly discussed herein, applicant is advised to note that the Angell reference is replete with species representative of substituted benzenes and pharmaceutical compositions of the formula (I). Consequently, any amendments to the claims to overcome rejections rendered under 35 U.S.C. § 103(a) should address this reference as a whole and should not be limited to the species discussed or disclosed explicitly herein.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Obviousness-type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute), so as to prevent the unjustified or improper timewise extension of the *right to exclude* granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). {See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969)}.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 12-15, 19-37 and 54-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 12-15, 19-37 and 54-57 of copending Application No. 10/898581. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 in the copending application recites definitions for *Y, X* and R^1 on the periphery of the aromatic core, which provide overlapping subject matter with respect to the instant claims. For example, if Y = -L-R^3, wherein L = -C(=O)NH, R^1 = lower alkyl; and X = -Ph-P in claim 1 of the copending application, then the genera of both the copending application and the instant application are identical. Furthermore, claim 37 of the instant application and claim 37 of copending Application No. 10/898581 recite identical species.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST.

The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DOUGLAS M WILLIS/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624